

## SCREENING-LEVEL HAZARD CHARACTERIZATION Cyclic Anhydrides Category

<b>Hexahydrophthalic anhydride (HHPA)</b>	<b>CASRN 85-42-7</b>
<b>Methylhexahydrophthalic anhydride (MHHPA)</b>	<b>CASRN 25550-51-0</b>
<b>Tetrahydrophthalic anhydride (THPA)</b>	<b>CASRN 85-43-8</b>
<b>Methyltetrahydrophthalic anhydride (MTHPA)</b>	<b>CASRN 34090-76-1/ 11070-44-3</b>
<b>Nadic methyl anhydride (NMA)</b>	<b>CASRN 25134-21-8</b>

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and

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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>	<p>85-42-7 25550-51-0 85-43-8 34090-76-1 11070-44-3 25134-21-8</p>
<p><b>Chemical Abstract Index Name</b></p>	<p>1,3-Isobenzofurandione, hexahydro- 1,3-Isobenzofurandione, hexahydromethyl- 1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro- 1,3-Isobenzofurandione, tetrahydro-5-methyl- 1,3-Isobenzofurandione, tetrahydromethyl- 4,7-Methanoisobenzofuran-1,3-dione, 3a,4,7,7a-tetrahydromethyl-, (3aR,4S,7R,7aS)-rel-]</p>
<p><b>Structural Formula</b></p>	<p><b>See Section 1</b></p>
<p style="text-align: center;"><b>Summary</b></p> <p>The cyclic anhydrides category contains both solid and liquid compounds that have moderate vapor pressure. The water solubility of the cyclic anhydrides cannot be accurately determined since the category members hydrolyze to their corresponding cyclic diacid rapidly. The cyclic anhydrides are expected to have high mobility in soil, but would hydrolyze to the cyclic diacid before traveling far. Volatilization of the cyclic anhydrides is expected to be low since these compounds hydrolyze rapidly to their corresponding cyclic diacid, which exist as anions in the environment. The rate of atmospheric photooxidation is considered rapid to moderate. The cyclic anhydrides are expected to have low persistence (P1) and low bioaccumulation potential (B1).</p> <p>The acute toxicity of the category members was low for the oral, dermal and inhalation routes. A combined repeated-dose/reproductive/developmental toxicity study by the oral routes in rats with CASRN 11070-44-3 showed histological changes in the forestomach at 300 mg/kg-bw/day; the NOAEL for systemic and maternal toxicity was 100 mg/kg-bw/day. There was no evidence</p>	

of reproductive or developmental toxicity and the NOAEL was 300 mg/kg-bw/day. CASRN 34090-76-1 did not induce gene mutations or structural chromosomal aberrations when tested *in vitro*. CASRNs 84-42-7, 85-43-8, 34090-76-1, and 25134-21-8 were slightly irritating to rabbit skin and severely irritating or corrosive to rabbit eyes. CASRN 85-43-8 was a skin sensitizer in guinea pigs. CASRNs 85-42-7 and 26590-20-5 were respiratory sensitizers in humans.

The 96-hour LC<sub>50</sub> of the cyclic anhydride category members to fish is >86 mg/L, the 48-hour EC<sub>50</sub> to aquatic invertebrates is 130 mg/L, and the 72-hour EC<sub>50</sub> to aquatic plants is 64 mg/L (biomass) and 68 mg/L (growth rate). The 21-day chronic reproduction EC<sub>50</sub> daphnia is 9.2 mg/L, and the NOEC and LOEC are 0.94 and 3.5 mg/L, respectively.

No data gaps were identified under the HPV Challenge Program.

The sponsor, the International Health Foundation Cyclic Anhydrides Committee and its member companies submitted a Test Plan and Robust Summaries to EPA for the cyclic anhydrides category on March 28, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on April 17, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/ihf/c12983tc.htm>). EPA comments on the original submission were posted to the website on September 26, 2001. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on November 13, 2001, December 20, 2001 and December 16, 2003 which were posted to the ChemRTK website on January 23, 2002, January 11, 2002 and February 24, 2004, respectively.

### **Category Justification**

Four members (HHPA, MHHPA, THPA, and MTHPA) of the cyclic anhydride category are bicyclic anhydrides, and NMA is a tricyclic anhydride. The category is based on similar chemical structures, physical-chemical properties, and toxicological properties. Although NMA's structure is more rigid than the other category members, the submitted physical and chemical properties and mammalian and ecotoxicity did not show major differences between

NMA and the rest of the members. EPA considered this grouping acceptable for the purposes of the HPV Challenge Program. Although treated as the same chemical in the HPV submission, for inventory purposes, EPA considers the two chemicals CASRN 34090-76-1 (1,3-isobenzofurandione, tetrahydro-5-methyl-) and CASRN 11070-44-3 (1,3-isobenzofurandione, tetrahydromethyl-) as separate entities/isomers. 1,3-isobenzofurandione, tetrahydromethyl- (CASRN 11070-44-3) has been evaluated under the OECD HPV Chemicals Program and published under UNEP (<http://www.chem.unep.ch/irptc/sids/OECDSEIDS/11070443.pdf>).

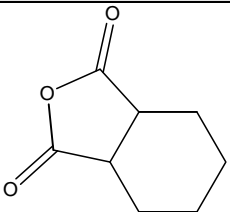
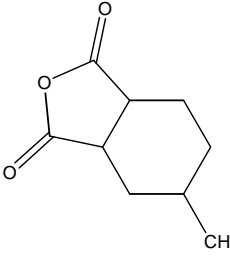
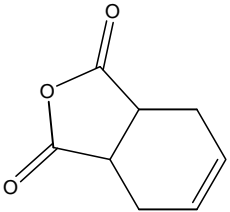
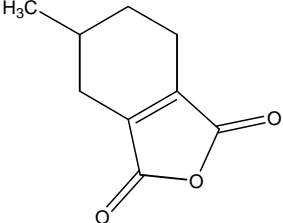
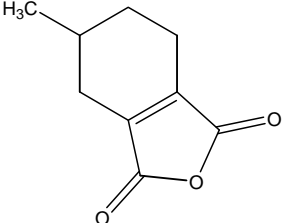
The IHF Consortium was contacted in August, 2009 to determine whether the testing proposed in their 2002 revised test plan had occurred. EPA learned that the Consortium had disbanded and was not planning on doing any further testing.

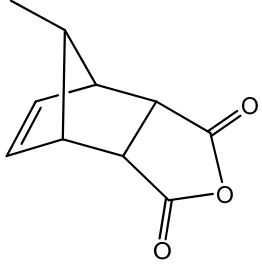
## **1 Chemical Identity**

### **1.1 Identification and Purity**

The following description is taken from the 2001 Test Plan and Robust Summary:

Chemicals in this category contain a bicyclic ring structure with the carboxylic acid anhydride group as the single reactive moiety that hydrolyzes to form the diacid in water. Two of the five bicyclic ring structures are saturated and three are partially unsaturated. One of the saturated and two of the partially unsaturated are substituted methyl derivatives. Compounds with the substituted methyl groups may exist as several isomeric forms. Test substance purity, when noted in the Robust Summaries, was given as  $\geq 99\%$ . The chemical structures of the cyclic anhydrides are depicted in Table 1.

Table 1: Cyclic Anhydrides Category Sponsored Chemical Structures		
Chemical Abstract Index Name	CASRN	Structure
1,3-Isobenzofurandione, hexahydro-	85-42-7	
1,3-Isobenzofurandione, hexahydromethyl-	25550-51-0	 Position of the methyl group is unspecified
1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydro-	85-43-8	
1,3-Isobenzofurandione, tetrahydro-5-methyl-	34090-76-1	
1,3-isobenzofurandione, tetrahydromethyl-	11070-44-3	 Position of the methyl group is unspecified

4,7-Methanoisobenzofuran-1,3-dione, 3a,4,7,7a-tetrahydro-methyl-, (3aR,4S,7R,7aS)-rel-	25134-21-8	 <p data-bbox="1193 430 1421 535">Position of the methyl group is unspecified</p>
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## 1.2 Physical-Chemical Properties

The physical-chemical properties of the cyclic anhydrides category are summarized in Table 2.

Property	Hexahydro-phthalic anhydride	Methylhexa-hydrophthalic anhydride	Tetrahydro-phthalic anhydride	Methyltetra-hydrophthalic anhydride	Nadic methyl anhydride
CASRN	85-42-7	25550-51-0	85-43-8	34090-76-1 (11070-44-3)	25134-21-8
Molecular Weight	154.16	168.19	152.15	166.17	178.18
Physical State	Glassy solid	Liquid	White crystalline powder <sup>2</sup>	Liquid	Colorless to light yellow viscous liquid <sup>2</sup>
Melting Point	34–38°C (measured) 37.5°C (cis, measured) <sup>5</sup> 144°C (trans, measured) <sup>5</sup>	-30°C (measured)	99–102°C (measured) 103-104°C (cis, measured) <sup>5</sup> 186°C (trans, measured) <sup>5</sup>	-38°C (measured for 34090-76-1) -5 to -3°C (measured for 19438-59-6) <sup>5</sup>	<-20°C (measured)
Boiling Point	285–296°C (measured) 158-160°C at 17 mm Hg (cis, 277°C NOMO5) <sup>5</sup> 125-135°C at 0.02 mm Hg (trans, 390°C NOMO5) <sup>5</sup>	299°C at 744 mm Hg (measured)	301°C (measured)	283–290°C (measured) 117-118°C at 2 mm Hg (measured for 19438-59-6, 281°C NOMO5) <sup>5</sup>	277°C at 743 mm Hg (measured) 140°C at 10 mm Hg (measured, 269°C NOMO5) <sup>4</sup>
Vapor Pressure	1.72×10 <sup>-3</sup> mm Hg at 20°C (estimated) 5×10 <sup>-3</sup> mm Hg at 25°C (NOMO5)	9.41×10 <sup>-4</sup> mm Hg at 20°C (estimated); 5 mm Hg at 137°C (measured) (0.003 mm Hg NOMO5)	1.32×10 <sup>-3</sup> mm Hg at 20°C (estimated)	2×10 <sup>-3</sup> mm Hg at 25°C (estimated) 3.5×10 <sup>-3</sup> mm Hg at 25°C (NOMO5)	9.88×10 <sup>-4</sup> mm Hg at 25°C (estimated)

Water Solubility	290–367 mg/L at 20°C (measured, hydrolyzes)	4700–4820 mg/L at 20°C (measured, hydrolyzes)	303–349 mg/L at 20°C (measured, hydrolyzes)	> 10g/L at 10°C (measured, likely the hydrolysis product)	105–146 mg/L at 20°C (measured, hydrolyzes)
Dissociation Constant (pK <sub>a</sub> )	4.43 (estimated for the cyclic diacid) <sup>3</sup>	4.43 (estimated for the cyclic diacid) <sup>3</sup>	4.43 (estimated for the cyclic diacid) <sup>3</sup>	4.43 (estimated for the cyclic diacid) <sup>3</sup>	4.14 (estimated for the cyclic diacid) <sup>3</sup>
Henry's Law Constant	2.1×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) <sup>4</sup>	2.9×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) <sup>4</sup>	1.9×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) <sup>4</sup>	1.0×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) <sup>4</sup>	1.5×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) <sup>4</sup>
Log K <sub>ow</sub>	2.17 (estimated)	2.59 (estimated)	1.96 (estimated)	4.0 (estimated) <sup>4</sup>	2.27 (estimated)

<sup>1</sup>The Industrial Health Foundation, Inc. Cyclic Anhydrides Committee. December 16, 2003. Revised Robust Summary and Test Plan for the Cyclic Anhydrides Category.

<http://www.epa.gov/chemrtk/pubs/summaries/ihf/c12983tc.htm>.

<sup>2</sup>HSDB. 2008. Hazardous Substances Data Bank. Accessed October 20, 2008. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.

<sup>3</sup>SPARC. 2008. Online pK<sub>a</sub> and Property Calculator v. 4.2.1405-s4.2.1408. Accessed October 20, 2008. <http://ibmlc2.chem.uga.edu/sparc/>.

<sup>4</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>5</sup>Beilstein, EV, volume 17/11, pages 76, 83, 134, 199. EIII/IV, volume 17, pages 5931, 5943, 5996, 6003. EII, volume 17, pages 452, 457. 19438-59-6 is 1,3-Isobenzofurandione, 4,5,6,7-tetrahydro-5-methyl-.

## **2 General Information on Exposure**

### **2.1 Production Volume and Use Pattern**

The cyclic anhydrides category chemicals had an aggregated production and/or import volume in the United States between 21.5 million pounds and 111.5 million pounds in calendar year 2005.

- CASRN 85-42-7 10 to 50 million pounds
- CASRN 2550-51-0 <500,000 pounds
- CASRN 85-43-8 1 to 10 million pounds
- CASRN 34090-76-1 10 to 50 million pounds
- CASRN 11070-44-3 <500,000 pounds
- CASRN 25134-21-8 500,000 to 1 million pounds

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include intermediates, adhesive and binding agents, coloring agents, dyes, and other. Non-confidential information in the IUR indicated that the commercial and consumer products containing the chemicals include adhesives and sealants, electrical and electronic products, fabrics, textile and apparel, and other. The HSDB states that tetrahydrophthalic anhydride (CASRN 85-43-8) is primarily used as a chemical intermediate for light-colored alkyds, polyesters, plasticizers and adhesives, as an anti-scorching agent in the rubber industry, and in the paints, lacquers and varnishes industry. Nadic methyl anhydride (CASRN 25134-21-8) is used as a chemical intermediate for polyester resins and a curing agent for epoxy resins. The

HPV submission states that these chemicals are primarily “destructive industrial use” chemicals and are not sold in consumer markets. Anhydrides are mainly used as curing agents (also called hardeners) in epoxy resin systems. Some of these chemicals are also used in the manufacture of alkyd and polyester resins.

## 2.2 Environmental Exposure and Fate

Although there is no quantitative information available on releases of these chemicals to the environment, there is potential for environmental releases to various media including water, land and air.

The environmental fate properties are provided in Table 3. The cyclic anhydrides are expected to have high mobility in soil, but will hydrolyze rapidly. The cyclic anhydrides were generally not readily biodegradable; however, these tests likely measured the lack of biodegradability of the hydrolysis products. Although the estimated Henry's Law constants suggest volatilization is moderate for the cyclic anhydrides, these compounds hydrolyze rapidly to their corresponding cyclic diacid, which exist as anions in the environment which do not volatilize. Due to the rapid rate of hydrolysis, the cyclic anhydrides are expected to have low persistence (P1) and low bioaccumulation potential (B1).

<b>Table 3. Environmental Fate Characteristics of Cyclic Anhydrides<sup>1</sup></b>					
<b>Property</b>	<b>Hexahydro-phthalic anhydride</b>	<b>Methylhexahydrophthalic anhydride</b>	<b>Tetrahydro-phthalic anhydride</b>	<b>Methyltetrahydrophthalic anhydride</b>	<b>Nadic methyl anhydride</b>
CASRN	85-42-7	25550-51-0	85-43-8	34090-76-1/ (11070-44-3)	25134-21-8
Photodegradation Half-life	37.7 hours (estimated)	30 hours (estimated)	1.04 hours (estimated)	6.3 hours(estimated on 34090-76-1) <sup>2</sup> 3.0 hours(estimated on 11070-44-3) <sup>2</sup>	1.04 hours (estimated)
Hydrolysis Half-life	<1 day at pH 4,7, and 9 at 25°C (measured)	<1 day at pH 4,7, and 9 at 25°C (measured)	<1 day at pH 4,7, and 9 at 25°C (measured)	Hydrolyzes to cyclic diacid	<1 day at pH 4,7, and 9 at 25°C (measured)
Biodegradation	1–6% after 28 days (not readily biodegradable)	0% after 28 days (not readily biodegradable)	0% after 28 days (not readily biodegradable); 21% after 21 days (not readily biodegradable)	No data	0% after 28 days (not readily biodegradable)
Bioconcentration	BCF = 9 (estimated) <sup>2</sup>	BCF = 20 (estimated) <sup>2</sup>	BCF = 6 (estimated) <sup>2</sup>	BCF = 203 (estimated on 34090-76-1) <sup>2</sup> BCF = 25 (estimated on 11070-44-3) <sup>2</sup>	BCF = 11 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	1 (estimated) <sup>2</sup>	1.2 (estimated) <sup>2</sup>	1 (estimated) <sup>2</sup>	2.7 (estimated on 34090-76-1) <sup>2</sup> 1.93 (estimated on 11070-44-3) <sup>2</sup>	1.5 (estimated) <sup>2</sup>
Fugacity (Level III Model)	4.47%	3.84%	0.205%	0.43%	0.192%
Air	40.6%	38.2%	43.9%	40.3%	41.7%
Water	54.8%	57.7%	55.7%	59.2%	57.9%
Soil	0.145%	0.229%	0.127%	0.09%	0.166%
Sediment					
Persistence <sup>3</sup>	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation <sup>3</sup>	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)

<sup>1</sup>The Industrial Health Foundation, Inc. Cyclic Anhydrides Committee. December 16, 2003. Revised Robust Summary and Test Plan for the Cyclic Anhydrides Category.

<http://www.epa.gov/chemrtk/pubs/summaries/ihf/c12983tc.htm>.

<sup>2</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v3.20. United States Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>3</sup>Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

### **3 Human Health Hazard**

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

#### ***Acute Oral Toxicity***

##### ***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

Sprague-Dawley rats (5/sex/dose) were administered HHPA via gavage at 1500, 2027, 2739, 3700, and 5000 mg/kg-bw and observed for 14 days. Mortality rates were 0/5, 0/5, 2/5, 5/5, and 5/5 males; and 1/5, 0/5, 3/5, 4/5, and 5/5 females for the 1500, 2027, 2739, 3700, and 5000 mg/kg-bw dose groups, respectively.

**LD<sub>50</sub> 3307 mg/kg-bw**

##### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 34090-76-1)***

Sprague-Dawley rats (5/sex/dose) were administered MTHPA via gavage at 0, 500, 1000, and 2000 mg/kg-bw and observed for 14 days. No mortality was seen at any dose.

**LD<sub>50</sub> > 2000 mg/kg-bw**

##### ***Nadic methyl anhydride (NMA) (CASRN 25134-21-8)***

Sprague-Dawley rats (5/sex/dose) were administered NMA via gavage at 650, 801, 987, 1217, and 1530 mg/kg-bw and observed for 14 days. Mortality was 1/10, 2/10, 4/10, 9/10 10/10 at 650, 801, 987, 1217, and 1530 mg/kg-bw, respectively. All deaths occurred within 6 days post-dosing.

**LD<sub>50</sub> = 958 mg/kg-bw**

#### ***Acute Dermal Toxicity***

##### ***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

New Zealand albino rabbits (5/sex) were administered HHPA dermally on abraded skin at 2000 mg/kg-bw under semi-occluded conditions for 24 hours and observed for 14 days. No rabbits died.

**LD<sub>50</sub> > 2000 mg/kg-bw**

##### ***Nadic methyl anhydride (NMA) (CASRN 25134-21-8)***

Ti<sub>F</sub>RAI<sub>f</sub> rats (5/sex/group) were administered NMA dermally at 2000, 3000, 4000, and 5000 mg/kg-bw for 24 hours and observed for 14 days. Mortality was 0/10, 2/10, 3/10, and 5/10 at 2000, 3000, 4000, and 5000 mg/kg-bw, respectively.

**LD<sub>50</sub> = 4920 mg/kg-bw**

##### ***Nadic methyl anhydride (NMA) (CASRN 25134-21-8)***

New Zealand albino rabbits (5/sex) were administered NMA dermally at 2000 mg/kg-bw for 24 hours and observed for 14 days. No mortality occurred.

**LD<sub>50</sub> > 2000 mg/kg-bw**

### *Acute Inhalation Toxicity*

#### ***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

Sprague-Dawley rats (5/sex/group) were exposed to HHPA aerosol for 4 hours at 1100 mg/m<sup>3</sup> (1.1 mg/L), a maximum attainable concentration, and observed for 15 days. No mortality occurred.

**LC<sub>50</sub> > 1.1 mg/L**

### *Repeated-Dose Toxicity*

#### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

In a combined repeated-dose/reproductive/developmental toxicity screening test, Sprague-Dawley rats (number/sex/dose unspecified) were administered tetrahydromethyl-1,3-isobenzofuranedione (CASRN 11070-44-3) via gavage at 0, 30, 100, and 300 mg/kg-bw/day for 49 days (males) or from 14 days prior to mating to day 3 of lactation (females). No changes were observed for body weight or food consumption. The only clinical sign of toxicity observed consisted of transient salivation at 300 mg/kg-bw/day. Hematology was unremarkable.

Decreases in total cholesterol and blood urea nitrogen, increases in triglycerides, and an increase in adrenal weights (relative/absolute;  $p < 0.05$ ) were reported at 300 mg/kg-bw/day in males only. Histopathological examination revealed changes in the forestomach. Forestomach changes characterized as moderate included squamous metaplasia of the forestomach observed in 10/12 males at 300 mg/kg-bw/day. Forestomach changes at 300 mg/kg-bw/day characterized as mild included squamous metaplasia of the forestomach in females (9/12 females), mucosal thickening of the forestomach in both sexes (10/12 males; 7/12 females), submucosal granulomatous inflammation (10/12 males; 7/12 females), epithelial vacuolar change (10/12 males; females not reported), edema (10/12 males; females not reported), cellular infiltration (1/12 males; 1/12 females), and erosion 1/12 males; 3/12 females). These details were found in the OECD document for CASRN 11070-44-3 at:

<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/11070443.pdf>.

**LOAEL (males/females) = 300 mg/kg-bw/day** (based on histopathological changes in the forestomach)

**NOAEL (males/females) = 100 mg/kg-bw/day**

### *Reproductive/Developmental Toxicity*

#### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

In the combined repeated-dose/reproductive/developmental toxicity screening test previously described, Sprague-Dawley rats were administered tetrahydromethyl-1,3-isobenzofuranedione (CASRN 11070-44-3) via gavage at 0, 30, 100, and 300 mg/kg-bw/day. No statistically significant effects were reported for any of the reproductive or developmental parameters/indices including estrous cyclicity, numbers of corpora lutea, implantations, gestation length, litter size, number of live newborns; and offspring sex ratios, body weight, viability, and gross external examinations.

**LOAEL (maternal) = 300 mg/kg-bw/day** (based on histopathological changes in the forestomach)

**NOAEL (maternal) = 100 mg/kg-bw/day**

**NOAEL (developmental toxicity) = 300 mg/kg-bw/day** (based on no adverse treatment-related effects at the highest dose tested)

**NOAEL (reproductive toxicity) = 300 mg/kg-bw/day** (based on no adverse treatment-related effects at the highest dose tested)

### ***Genetic Toxicity – Gene Mutations***

#### ***In vitro***

##### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 34090-76-1)***

*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and in *Escherichia coli* Wp2 uvrA were exposed to MTHPA at 0, 62.5, 125, 250, 500, 1000, and 2000 µg/plate, without metabolic activation and 0, 156, 313, 625, 1250, 2500, and 5000 µg/plate with metabolic activation. Positive controls were run concurrently. Cytotoxicity was evident at 500 µg/plate (TA1535), 1000 µg/plate (TA100, TA98, TA1537), and 2500 µg/plate (*E. coli* Wp2 uvrA) without activation, and at 5000 µg/plate in TA100 and TA1537 with activation. Positive control responses were not provided in the robust summary. No mutagenicity was observed.

**MTHPA was not mutagenic in this assay.**

### ***Genetic Toxicity – Chromosomal Aberrations***

#### ***In vitro***

##### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 34090-76-1)***

Chinese hamster lungs cells, CHL/IU, were exposed to MTHPA at 0.075, 0.15 and 0.30 mg/mL by continuous treatment in the presence and absence of metabolic activation. In a short-term treatment assay without metabolic activation, the cells were exposed to MTHPA at 0.05, 0.10 and 0.20 mg/mL and at 0.11, 0.21 and 0.43 mg/mL with metabolic activation. Positive controls were used. Cytotoxic concentrations were 0.30 mg/mL for continuous treatment with activation, 0.40 mg/mL in short-term assay without metabolic activation, and 1.0 mg/mL with metabolic activation. Structural chromosomal aberrations were not induced following 24 hours of continuous treatment. Weak polyploidy was induced in short-term assays.

**MTHPA did not induce structural chromosomal aberrations in this assay.**

### ***Additional Information***

#### ***Skin irritation***

##### ***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

Six New Zealand albino rabbits (sex not reported) were administered 6.25, 12.5, 25 and 50% HHPA dermally and were scored at 24 and 72 hours according to the Draize scale. Minimal to slight irritation was seen at ≤ 50%.

**HHPA was slightly irritating to rabbit skin.**

##### ***Tetrahydrophthalic anhydride (THPA) (CASRN 85-43-8)***

Rabbits (strain and number not stated) were administered THPA on to the skin. No irritation was noted.

**THPA was not irritating to skin.**

***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 34090-76-1)***

In one test in rabbits, MTHPA was shown to be slightly irritating to the skin. No other details were provided.

**MTHPA was slightly irritating to rabbit skin.**

***Nadic methyl anhydride (NMA) (CASRN 25134-21-8)***

Two separate tests in rabbits with NMA, one using a 50% suspension and the other an undiluted solution, showed slight to moderate irritation to the skin, respectively.

**NMA was slightly to moderately irritating to rabbit skin.**

***Eye irritation***

***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

In a Draize test, 12 New Zealand white rabbits (sex not reported) were instilled with 100 mg HHPA into the eyes. The eyes of six rabbits were not washed and the eyes of three rabbits each were either washed for 4 or 30 seconds. Unwashed eyes and those washed at 30 seconds showed severe irritation and corrosion with no recovery at 21 days. Rabbits at 4 seconds showed severe but reversible irritation by 19 days.

**HHPA was severely irritating or corrosive to rabbit eyes.**

***Tetrahydrophthalic anhydride (THPA) (CASRN 85-43-8)***

In an acute eye irritation/corrosion study in rabbits, THPA was shown to be corrosive to the eyes. No scores were calculated since only one test animal was used.

**THPA was corrosive to rabbit eyes.**

***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 34090-76-1)***

In a Draize test in rabbits, MTHPA was shown to be highly irritating to the eyes. No other details were provided.

**MTHPA was irritating to rabbit eyes.**

***Nadic methyl anhydride (NMA) (CASRN 25134-21-8)***

In two tests, NMA was shown to be highly corrosive (no washout) or irritating (4 second washout) to rabbit eyes.

**NMA is corrosive to rabbit eyes.**

***Skin sensitization***

***Tetrahydrophthalic anhydride (THPA) (CASRN 85-43-8)***

In a guinea pig maximization test, THPA was shown to be sensitizing, with 17/20 guinea pigs showing a positive response.

**THPA was a skin sensitizer in guinea pigs.**

*Respiratory sensitization (These summaries reflect EPA reviews of the cited literature and not the robust summaries provided in the HPV Challenge Program submission)*

***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7); Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 26590-20-5)<sup>4</sup>***

A total of 110 workers (54 men, 56 women; 19-58 years old) employed at a medium-sized company for an average of 8.1 years were investigated (Drexler et al., 1994). The employees received extensive medical evaluations after 4 workers reported obstructive respiratory tract diseases suggesting that some workers were sensitized to HHPA and/or MTHPA. The reproductive status of the women was not reported in the study. The employees participated in the study on a voluntary basis; 20% of workers chose to not participate in the investigation. No reference is made regarding informed consent. The investigators collected information about the workers' clinical symptoms related to allergies and/or respiratory problems (e.g. rhinitis, rhinoconjunctivitis, dry cough, asthma symptoms). Sera were obtained and subsequently total IgE levels and specific IgE to common allergens, HHPA, MTHPA, TMA or HAS conjugates of phthalic anhydride (PA) were measured with the RAST assay. Skin prick tests were also conducted with the following allergens: PA, histamine (positive control), acetone (negative control), HHPA or MTHPA. An inhalation challenge test was performed with employees who reported suspected clinical symptoms related to an occupational allergy and showed a positive skin prick test and/or a RAST with PA conjugates. For the inhalation challenge, the employees handled HHPA and MTHPA in a small room for about 10 min under conditions mimicking the normal workplace environment. During the exposure, inhalation exposure was avoided and a medical doctor monitored the workers. In addition, the physician provided a medical evaluation after the exposure which included a whole-body plethysmography.

A total of 17 workers had specific IgE against HHPA and/or MTHPA. Six workers showed clinically relevant symptoms (e.g. rhinitis, increased air way resistance) in the challenge test. Data from the RAST and skin prick tests showed that both methods could be used to evaluate the workplace-related sensitization to HHPA and MTHPA.

**HHPA and MTHPA were respiratory sensitizers in humans.**

***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

A total of 81 workers exposed to HHPA while preparing an epoxy resin product were studied (Grammer et al., 1995). The age and gender of the workers was not specified. All subjects identified by the chemical plant management as HHPA-exposed workers agreed to participate in the study and informed consent was obtained. The investigators evaluated the history of occupational immunologic lung disease by questionnaire, spirometry and chest film. Blood samples were collected to measure specific IgE and IgG antibodies against HHP-HSA by ELISA. Those workers that had a positive ELISA and/or the presence of HHPA-related respiratory symptoms were interviewed, examined and skin tested with HHP-HAS.

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<sup>4</sup> The submitter provided data from the published literature indicating that cyclic anhydrides as a class are respiratory sensitizers. Some of the information is based on chemicals not part of this category, but which are close analogs, including CASRN 26590-20-5, CA Index Name 1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydromethyl-

Antibodies against HHP-HSA were detected in 14 workers reporting IgE- and/or IgG-mediated disease; the remaining 67 workers had no disease and no detectable response against the HHP-HSA conjugate. The authors used the Univariable Optimal Discriminant Analysis (ODA) model to study whether the antibody levels could be used to predict an immunologically-mediated respiratory disease. Based on the results of the model, the authors concluded that HHPA workers with high antibody titers (IgE or IgG) would have a significant likelihood of exhibiting an immunologically-mediated respiratory condition.

**HHPA was a respiratory sensitizer in humans.**

***Hexahydrophthalic anhydride (HHPA) (CASRN 85-42-7)***

A total of 33 subjects (20-58 years old; gender not specified) employed in a plant manufacturing components for the electronic industry were studied (Nielsen et al., 1994). Additional details on the recruitment process were not provided in the report. No reference is made regarding informed consent.

Thirteen workers tested positive for sensitization against HHPA; the remaining 20 subjects tested negative for sensitization, although 9 workers showed symptoms associated with an acid anhydride allergy. The investigators evaluated the medical and occupational history of the workers by questionnaire and skin prick tests. Prior to the challenge test, the investigators recorded the exposure to HHPA, smoking habits and current clinical symptoms as well as conducted a physical examination and a skin prick test against HHPA-HAS. Blood samples were collected to measure specific IgE and IgG antibodies by RAST and ELISA. For the nasal challenge test, a mist of HHPA-HSA solution was sprayed into each worker's nostrils. Nasal symptoms, nasal inspiratory peak flow and nasal lavage were recorded before and after the challenge test. Nasal lavage fluid was used for tests measuring tryptase, eosinophil cationic protein, myeloperoxidase and albumin.

Eleven workers who were IgE-sensitized against HHPA and reported clinical symptoms demonstrated a decrease in nasal inspiratory peak flow and an increase in nasal symptoms after the challenges. Although not explicitly stated, the report suggested that the nasal symptoms were reversible. Workers who were IgE-sensitized against HHPA showed a significant elevation of eosinophil and neutrophil counts as well as an increase in the levels of tryptase and albumin. No significant changes were reported for eosinophil cationic protein. The non-sensitized workers did not exhibit significant changes in the parameters measured in the study. These observations suggested a possible role of IgE in the HHPA-mediated sensitization in humans. The study did not show a role of IgG antibodies in the pathomechanism of the HHPA sensitization.

**HHPA was a respiratory sensitizer in humans.**

**Conclusion:** The acute toxicity of the category members was low for the oral, dermal and inhalation routes. A combined repeated-dose/reproductive/developmental toxicity study by the oral routes in rats with CASRN 11070-44-3 showed histological changes in the forestomach at 300 mg/kg-bw/day; the NOAEL for systemic and maternal toxicity was 100 mg/kg-bw/day. There was no evidence of reproductive or developmental toxicity and the NOAEL was 300 mg/kg-bw/day. CASRN 34090-76-1 did not induce gene mutations or structural chromosomal aberrations when tested *in vitro*. CASRNs 84-42-7, 85-43-8, 34090-76-1, and 25134-21-8 were slightly irritating to rabbit skin and severely irritating or corrosive to rabbit eyes. CASRN 85-43-

8 was a skin sensitizer in guinea pigs. CASRNs 85-42-7 and 26590-20-5 were respiratory sensitizers in humans.

<b>Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data</b>					
<b>Endpoints</b>	<b>Hexahydro-phthalic anhydride (HHPA) (85-42-7)</b>	<b>Methylhexa-hydrophthalic anhydride (MHHPA) (25550-51-0)</b>	<b>Tetra-hydro-phthalic anhydride (THPA) (85-43-8)</b>	<b>Methyltetra-hydrophthalic anhydride (MTHPA) (34090-76-1/ 11070-44-3)<sup>1</sup></b>	<b>Nadic methyl anhydride (NMA) (25134-21-8)</b>
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>3307</b>	No Data > 2000 (RA)	No Data > 2000 (RA)	<b>&gt; 2000</b>	<b>958</b>
<b>Acute Dermal Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 2000</b>	No Data > 2000 (RA)	No Data > 2000 (RA)	No Data > 2000 (RA)	<b>&gt; 2000 - 4920</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>&gt; 1.1</b>	No Data > 1.1 (RA)	No Data > 1.1 (RA)	No Data > 1.1 (RA)	No Data > 1.1 (RA)
<b>Repeated-Dose Toxicity NOAEL/LOAEL (mg/kg-bw/day)</b>	No Data NOAEL = 100 LOAEL = 300 (RA)	No Data NOAEL = 100 LOAEL = 300 (RA)	No Data NOAEL = 100 LOAEL = 300 (RA)	<b>NOAEL = 100 LOAEL = 300</b>	No Data NOAEL = 100 LOAEL = 300 (RA)
<b>Reproductive Toxicity NOAEL/LOAEL (mg/kg-bw/day)</b>	No Data NOAEL = 300 (RA)	No Data NOAEL = 300 (RA)	No Data NOAEL = 300 (RA)	<b>NOAEL = 300 (hdt)</b>	No Data NOAEL = 300 (RA)
<b>Developmental Toxicity NOAEL/LOAEL (mg/kg-bw/day) Maternal toxicity</b>	No Data NOAEL = 100 LOAEL = 300	No Data NOAEL = 100 LOAEL = 300  NOAEL = 300	No Data NOAEL = 100 LOAEL = 300	<b>NOAEL = 100 LOAEL = 300  NOAEL = 300 (hdt)</b>	No Data NOAEL = 100 LOAEL = 300
<b>Developmental Toxicity</b>	NOAEL = 300 (RA)	(RA)	NOAEL = 300 (RA)		NOAEL = 300 (RA)

<b>Table 4. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Human Health Data</b>					
<b>Endpoints</b>	<b>Hexahydro-phthalic anhydride (HHPA) (85-42-7)</b>	<b>Methylhexahydro-phthalic anhydride (MHHPA) (25550-51-0)</b>	<b>Tetra-hydro-phthalic anhydride (THPA) (85-43-8)</b>	<b>Methyltetra-hydrophthalic anhydride (MTHPA) (34090-76-1/ 11070-44-3)<sup>1</sup></b>	<b>Nadic methyl anhydride (NMA) (25134-21-8)</b>
<b>Genetic Toxicity – Gene Mutations <i>In vitro</i></b>	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	<b>Negative</b>	No Data Negative (RA)
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i></b>	No Data Negative (RA)	No Data Negative (RA)	No Data Negative (RA)	<b>Negative</b>	No Data Negative (RA)
<b>Additional Information</b>					
<b>Skin Irritation</b>	<b>Slightly irritating</b>	–	<b>Not irritating</b>	<b>Slightly irritating</b>	<b>Slightly to moderately irritating</b>
<b>Eye Irritation</b>	<b>Highly irritating to corrosive</b>	–	<b>Corrosive</b>	<b>Irritating</b>	<b>Irritating to highly corrosive</b>
<b>Skin Sensitization</b>	Positive	Positive	<b>Positive</b>	–	–
<b>Respiratory Sensitization</b>	<b>Positive</b>	–	–	<b>Positive</b>	–

Measured data in bold text; (RA) = Read Across; (hdt) = highest dose tested

<sup>1</sup> Data from OECD HPV Chemicals Program (<http://www.chem.unep.ch/irptc/sids/OECD/SIDS/11070443.pdf>) were used because the documents are more recent than the November 2001 test plan.

#### **4 Hazards to the Environment**

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

##### ***Acute Toxicity to Fish***

##### ***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

(1) Japanese medaka (*Oryzias latipes*) were exposed to methyltetrahydrophthalic anhydride at nominal concentrations of 0 or 100 mg/L under flow-through conditions for 96 hours. The measured concentrations were within 20% of the nominal concentration; however, the LC<sub>50</sub> was expressed based on the nominal concentration. The pH at 100 mg/L was 6.3-6.4, possibly due to the hydrolysis.

**96-h LC<sub>50</sub> > 100 mg/L**

(2) Japanese medaka (*Oryzias latipes*) were exposed to methyltetrahydrophthalic anhydride at nominal concentrations of 0 or 100 mg/L under flow-through conditions for 14 days. The pH at 100 mg/L varied from 6.3 to 6.6, possibly due to the hydrolysis.

**96-h LC<sub>50</sub> > 86 mg/L**

***Acute Toxicity to Aquatic Invertebrates***

***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

Water fleas (*Daphnia magna*) were exposed to methyltetrahydrophthalic anhydride at nominal concentrations of 0, 32, 56, 100, 180, and 320 mg/L under static conditions for 48 hours. The mean measured concentrations were 0, 31, 49, 87, 140, and 270 mg/L. The pH for test substance concentrations up to 140 mg/L ranged from 5.6 to 7.8, possibly due to hydrolysis. At 270 mg/L, the pH was 4.3 at the beginning of the test and was not measured at the end of the test; all *Daphnids* at this concentration died by the end of the test.

**48-h EC<sub>50</sub> = 130 mg/L**

***Toxicity to Aquatic Plants***

***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

Green algae (*Pseudokirchneriella subcapitata*) were exposed to methyltetrahydrophthalic anhydride at nominal concentrations of 0, 10, 18, 32, 56, and 100 mg/L under static conditions for 72 hours. The mean measured concentrations were 0, 9, 15, 28, 49, and 86 mg/L. The pH for the test substance concentrations up to 56 mg/L ranged from 5.2 to 7.8, and was lower at 100 mg/L, possibly due to hydrolysis.

**72-h EC<sub>50</sub> (growth rate) = 68 mg/L**

**72-h EC<sub>50</sub> (biomass) = 64 mg/L**

***Chronic Toxicity to Aquatic Invertebrates***

***Methyltetrahydrophthalic anhydride (MTHPA) (CASRN 11070-44-3)***

Water fleas (*Daphnia magna*) were exposed to methyltetrahydrophthalic anhydride at nominal concentrations of 0, 1.3, 4.1, 13, 41 and 130 mg/L for 21 days in a reproduction toxicity test. Concentrations were measured at preparation and before renewal on both day 9 and day 16. Time-weighted mean measured concentrations were < 0.2, 0.94, 3.5, 11, 35, and 110 mg/L. The pH varied from 6.1 to 8.2.

**EC<sub>50</sub> (21-day, reproduction) = 9.2 mg/L**

**NOEC (21-day, reproduction rate) = 0.94 mg/L**

**LOEC (21-day, reproduction rate) = 3.5 mg/L**

**Conclusion:** The 96-hour LC<sub>50</sub> of the cyclic anhydride category members to fish is >86 mg/L, the 48-hour EC<sub>50</sub> to aquatic invertebrates is 130 mg/L, and the 72-hour EC<sub>50</sub> to aquatic plants is 64 mg/L (biomass) and 68 mg/L (growth rate). The 21-day chronic reproduction EC<sub>50</sub> daphnia is 9.2 mg/L, and the NOEC and LOEC are 0.94 and 3.5 mg/L, respectively.

**Table 5. Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program: Aquatic Toxicity Data**

Endpoints	Hexahydro-phthalic anhydride (HHPA) (85-42-7) <sup>1</sup>	Methylhexa-hydro-phthalic anhydride (MHHPA) (25550-51-0) <sub>1</sub>	Tetrahydro-phthalic anhydride (THPA) (85-43-8) <sup>1</sup>	Methyltetra-hydro-phthalic anhydride (MTHPA) (34090-76-1)	Methyltetra-hydro-phthalic anhydride (MTHPA) (11070-44-3) <sub>2</sub>	Nadic methyl anhydride (NMA) (25134-21-8) <sub>3</sub>
<b>Fish</b> <b>96-h LC<sub>50</sub></b> <b>(mg/L)</b>	No Data > 86 (RA)	No Data > 86 (RA)	No Data > 86 (RA)	No Data > 86 (RA)	<b>&gt; 86</b>	No Data > 86 (RA)
<b>Aquatic Invertebrates</b> <b>48-h EC<sub>50</sub></b> <b>(mg/L)</b>	No Data 130 (RA)	No Data 130 (RA)	No Data 130 (RA)	No Data 130 (RA)	<b>130</b>	No Data 130 (RA)
<b>Aquatic Plants</b> <b>72-h EC<sub>50</sub></b> <b>(mg/L)</b> <b>(growth rate)</b> <b>(biomass)</b>	No Data 68 64 (RA)	No Data 68 64 (RA)	No Data 68 64 (RA)	No Data 68 64 (RA)	<b>68</b> <b>64</b>	No Data 68 64 (RA)
<b>Chronic Toxicity to Aquatic Invertebrates</b> <b>21-day EC<sub>50</sub>/</b> <b>LOEC/NOEC</b> <b>(mg/L)</b>	No Data 9.2 3.5/0.94 (RA)	No Data 9.2 3.5/0.94 (RA)	No Data 9.2 3.5/0.94 (RA)	No Data 9.2 3.5/0.94 (RA)	<b>9.2</b> <b>3.5/0.94</b>	No Data 9.2 3.5/0.94 (RA)

**bold = measured data (i.e., derived from testing)**; <sup>1</sup>Sponsor withdrew the ecotoxicity data in their revised test plan based on earlier EPA comments about the inadequacy of the information; <sup>2</sup>Data from published SIDS documents <http://www.chem.unep.ch/irpte/sids/OECD/SIDS/11070443.pdf>; toxicity should reflect hydrolysis products because the parent was stirred for > 1 hr; <sup>3</sup>The sponsor proposed testing for this compound.

## **5 References**

Drexler, H., A. Weber, S. Letzel, G. Kraus, K. H. Schaller, and G. Lenhert. 1994. Detection and clinical relevance of a type I allergy with occupational exposure to hexahydrophthalic anhydride and methyltetrahydrophthalic anhydride. *Int Arch Occup Environ Health* 65 (5):279-83.

Grammer, L. C., M. A. Shaughnessy, M. B. Hogan, S. M. Berggruen, D. M. Watkins, and P. R. Yarnold. 1995. Value of antibody level in diagnosing anhydride-induced immunologic respiratory disease. *J Lab Clin Med* 125 (5):650-3.

Nielsen, J., H. Welinder, H. Ottosson, I. Bensryd, P. Venge, and S. Skerfving. 1994. Nasal challenge shows pathogenetic relevance of specific IgE serum antibodies for nasal symptoms caused by hexahydrophthalic anhydride. *Clin Exp Allergy* 24 (5):440-9.